REMARKS

I. INTRODUCTION

Receipt of the Office Action of April 14, 2004 is acknowledged. Applicants appreciate the acknowledgement that claims 1, 2, 4, 5, 9-12 and 15 are allowable over the prior art. It is respectfully requested that the Examiner indicate the status of claim 24 which is listed page 2 of the Office Action as pending, but has not been indicated as pending, allowed or rejected in the "Disposition of the Claims."

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 1, 2, 4, 5, 9-12, 15-16, 18-22 and 24 are pending in this application.

II. THE OFFICE ACTION

Rejection based on 35 U.S.C. § 112, first paragraph-Enablement

The Examiner has rejected claims 16 and 18-22 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement for treatment of a "protein kinase related disorder." Applicants respectfully traverse.

While the Examiner has addressed the factors of *In re Wands*, it appears that she has not considered the lengthy discussion of *in vitro* assays, synthesis examples and *in vivo* animal model testing in the specification.

Applicants contend that both the synthetic examples and the biological examples, both *in vitro* and *in vivo*, in the specification provide sufficient evidence to establish enablement for the reasons that follow.

A. Nature of the Invention

The nature of the present invention relates to organic chemistry and the compounds of the invention can be prepared using classic techniques found in organic chemistry and prepared by the synthetic protocols herein. The claimed invention relates to the use of the compounds as inhibitors of protein kinases for treating disorders associated with protein kinases.

B. *State of the Art*

The state of the prior art is such that compounds similar to those claimed in the present application have been prepared and used in pharmaceutical applications, see, e.g., WO 92/20642. It is well established that compounds that inhibit protein kinases are useful for treating disorders resulting from aberrant protein kinase activity.

C. *Level of Ordinary Skill in the Art*

The relative skill in the art relates to routine practices of the skilled worker. In the present field, the skilled worker would have to be able to synthesize the compounds of claim 1 and be able to treat a protein kinase related disorder. The present specification describes the knowledge level of one having ordinary skill in the art in the "Background of the Invention."

D. *Level of Predictability*

The level of predictability in the art is another factor to consider. Where there is unpredictability in the art, e.g., in determining whether a compound is an antagonist or an agonist, one skilled in the art would rely on teachings in the specification as well as teachings of scholarly journals. Here, the specification provides a means for determining whether a compound modulates the function of protein kinase. *See* pages 160-222 for in vitro tests and pages 222-231 for in vivo tests.

E. *Amount of Direction and Guidance in the Specification*

The fifth factor involves amount of direction provided by the inventor. Here, the inventor has provided ample disclosure of how to prepare the compounds and use them as inhibitors of protein kinase activity. Moreover, there are numerous examples of compounds of claim 1 prepared according to the disclosure of the present application. Furthermore, IC_{50} values are given for a large number of claimed compounds. Thus, the inventors not only teach how to make the compounds, but also teach how to test the compounds for PK inhibition. The skilled artisan would therefore know which compounds would be useful for treating PK related disorders based on the teachings in the specification.

F. Existence of Working Examples

The presence of working examples is the sixth prong of the test and the present specification provides examples of how to make and use the presently claimed invention.

The Examiner contents that factors five and six find support in the specification only at page 31, lines 19-29 and pages 32-39, page 40, lines 1-7 and pages 41-47. However, this is incorrect. The Examiner's attention is directed to over 60 examples of compounds which are prepared using the organic chemistry synthesis protocols described in the present specification at pages 98-160. In addition, the present specification provides biological evaluation assays at pages 160-222 and includes protocols for the following assays: FLK-1, EGFR-HER2, PDGF-R, IGF-1, EGFR, Met autophosphorylation, src, lck, phosphorylating function of RAF, CDK/Cyclic A, PDGF induced BrdU, EGF induced BrdU, EGF induced HER2 driven BrdU, IGF 1 induced BrdU, FGF induced BrdU, biochemical EGFR, biochemical PDGFR, biochemical FGFR, biochemical FLK-1 and HUV-EC-C assay. The biological information is not limited to *in vitro* tests, rather, *in vivo* xenograft models also are described on pages 222-231.

G. Breadth of the Claims

The seventh factor is the breadth of the claims. The Examiner asserts that there are a large number of disorders encompassed by the present claim. It is respectfully submitted that just because a large number of disorders may be encompassed by the claims, does not necessitate a lack of enablement.

Additionally, while Applicants understand that the rejection is premised on lack of enablement, the Guidelines published by Deputy Commissioner for Patent Policy on Utility (35 U.S.C. § 101) are relevant where it states:

> Office personnel should explain why any in vitro or in vivo data supplied by the applicant would not be reasonably predictive of an asserted therapeutic utility from the perspective of a person of ordinary skill in the art.
>
> . . . As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. An applicant can establish this reasonable correlation by

> relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use (*emphasis added*).

Based on this position by the Deputy Commission for Patent Policy, the synthetic information and assay data and *in vivo* model employed would appear to adequately enable the present claims.

H. *Quantity of Experimentation needed to make or use the invneiton basedo n the content of the disclosure*

The last factor is the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Here, the disclosure provides guidance on how to make the compounds on pages 98-160. In addition, the present specification provides biological evaluation assays at pages 160-222 and includes protocols for the following assays: FLK-1, EGFR-HER2, PDGF-R, IGF-1, EGFR, Met autophosphorylation, src, lck, phosphorylating function of RAF, CDK/Cyclic A, PDGF induced BrdU, EGF induced BrdU, EGF induced HER2 driven BrdU,, IGF 1 induced BrdU, FGF induced BrdU, biochemical EGFR, biochemical PDGFR, biochemical FGFR, biochemical FLK-1 and HUV-EC-C assay. The biological information is not limited to *in vitro* tests, rather, *in vivo* xenograft models also were employed as found at pages 222-231.

As in *Wands*, a high level of skill existed at the time of filing with the methods needed to practice the invention. Knowledge of synthetic organic chemistry was well known at the time of filing. Applicants have provided ample evidence that the level of skill in preparing small molecules according to claim 1 was highly developed as of the filing date of the application along with their protein kinase inhibitory activity. Thus, applicants have provided sufficient evidence to enable one of ordinary skill in the art to practice, without undue experimentation, the claimed invention.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Objection to the specification

The Examiner's objection to the specification is noted. The graphs have been deleted from the text of the specification, pages 227 and 228, and have been added as drawings. See the attached Proposed Drawing Correction. A section entitled "Brief Description of the Drawings" has been added to the specification. No new matter has been added by this amendment.

III. CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

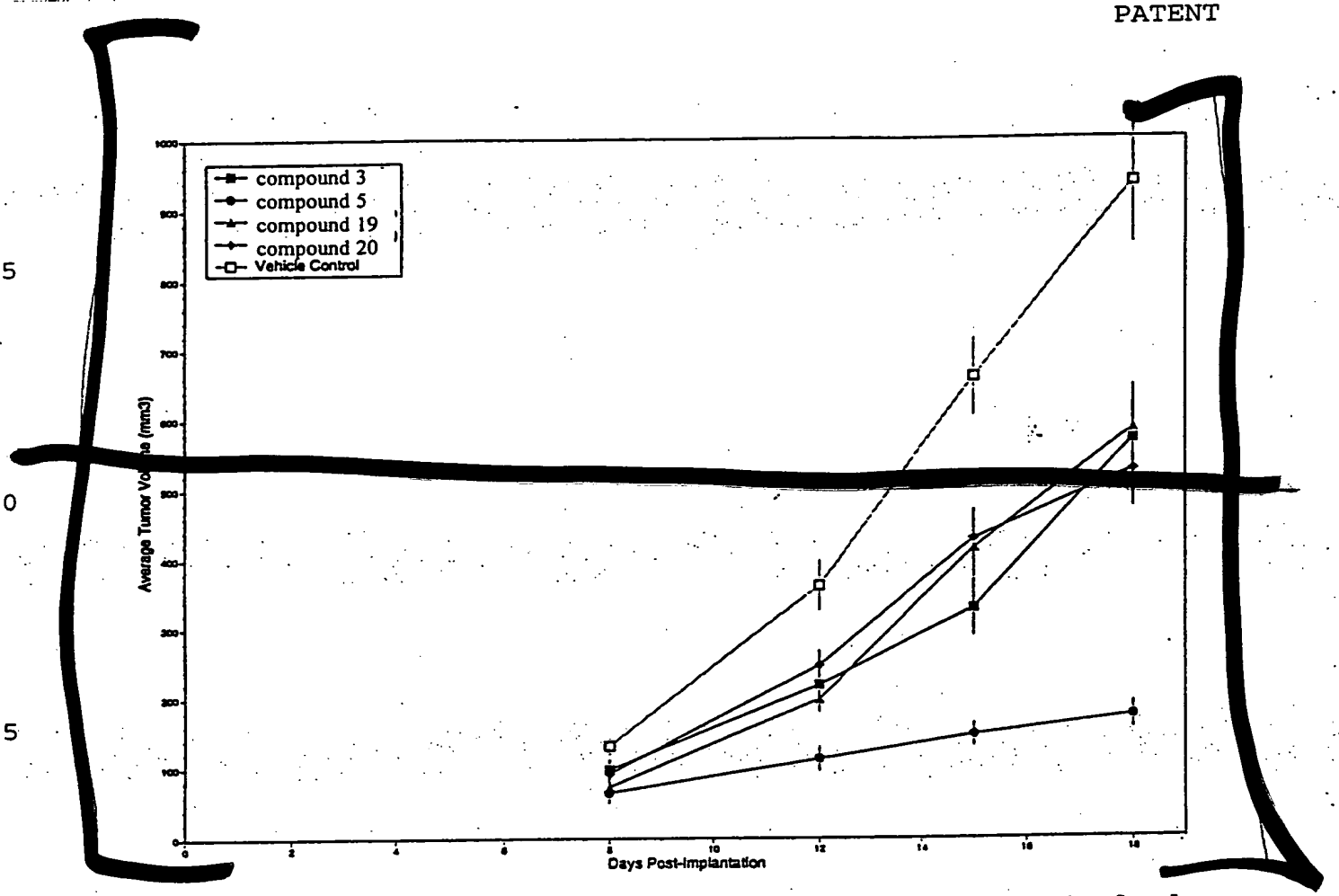
Date July 14, 2004

By _____

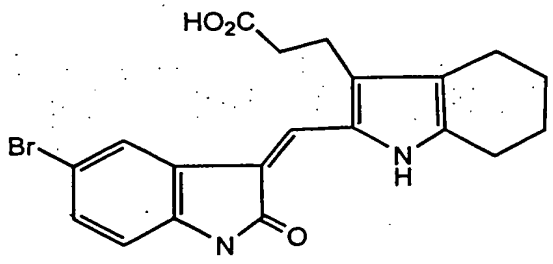
FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5475
Facsimile: (202) 672-5399

Beth A. Burrous
Attorney for Applicant
Registration No. 35,087

Reg. #41,545



The unexpected efficacy of compound 5 in vivo, particularly upon oral administration, is further demonstrated when it is compared to compound 65:

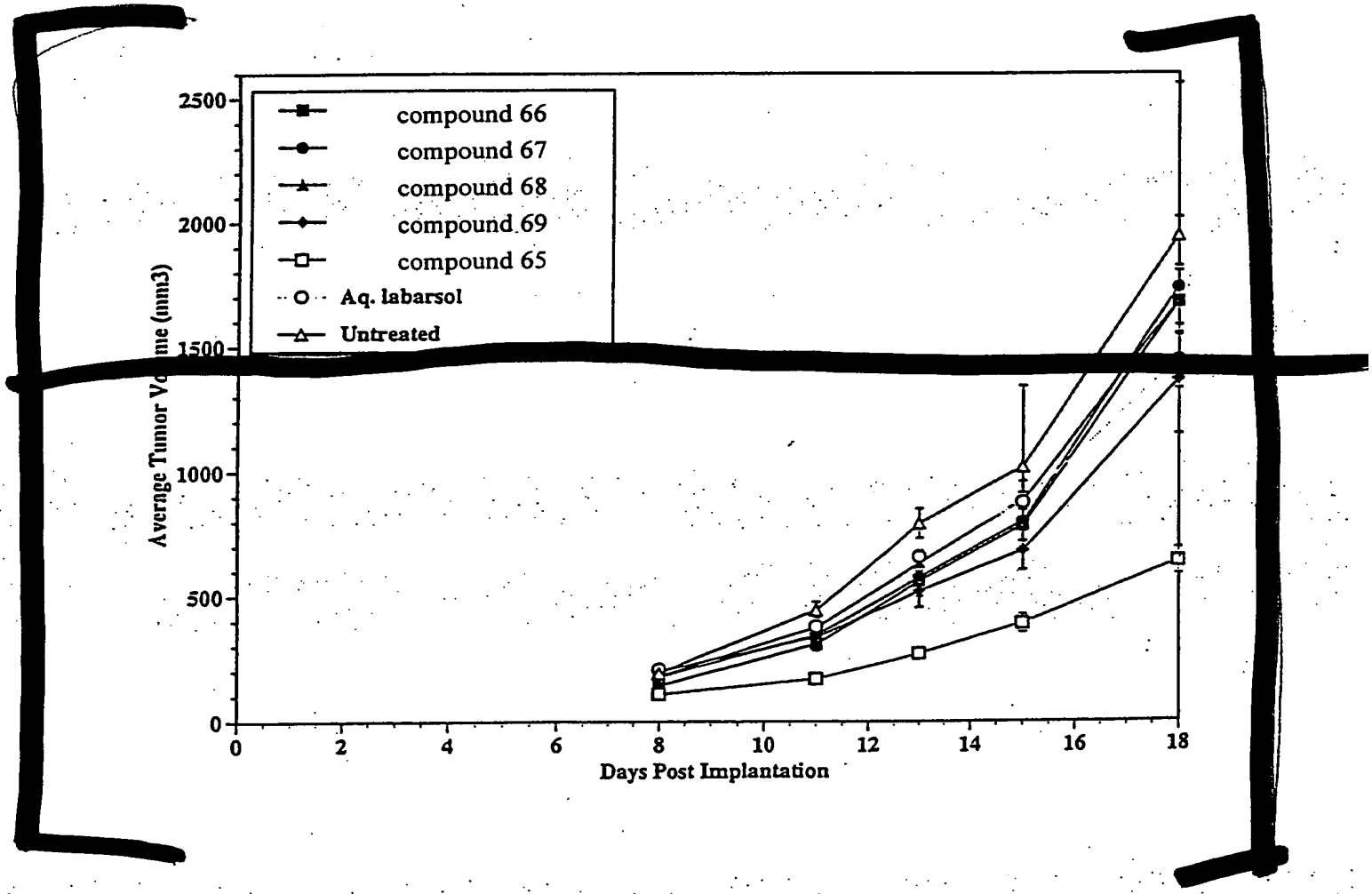


65

Compound 65 manifests almost an order of magnitude greater potency in vitro than compound 5 (data not shown). However, when

tested interpertitoneally in mice against two different tumor cells lines, SF763T and SF767T, compound 5 is from slightly (5% greater inhibition at 21 days) to notably (14% greater inhibition at 21 days) more efficacious than compound 65.

The difference in activity between compound 5 and compound 65 is even greater when the two compounds are administered orally. The oral efficacy of compound 65 and several of its analogs, compounds 66 - 69, is shown graphically below:



Title: PYRROLE SUBSTITUTED 2-INDOLINONE PROTEIN KINASE INHIBITORS
Inventor(s): Pen Cho TANG et al.
Appl. No.: 10/081,147

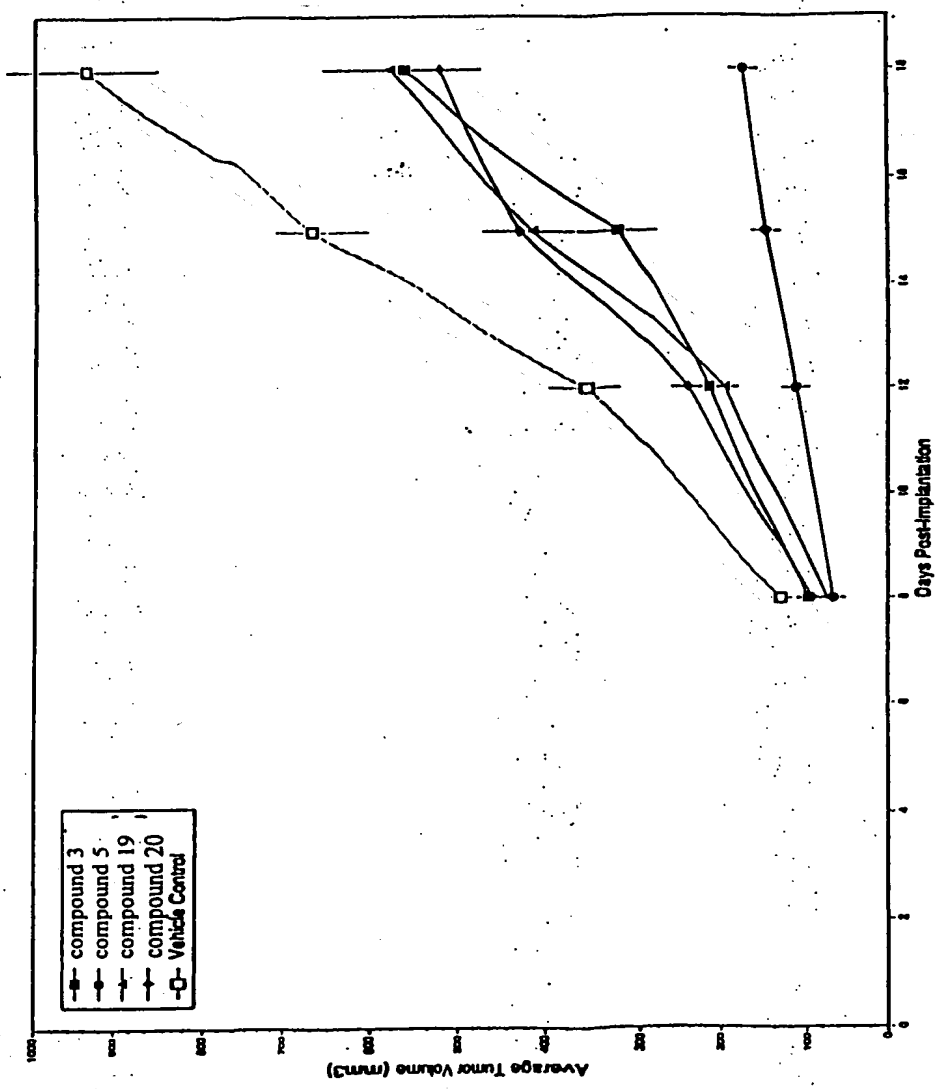


FIGURE 1

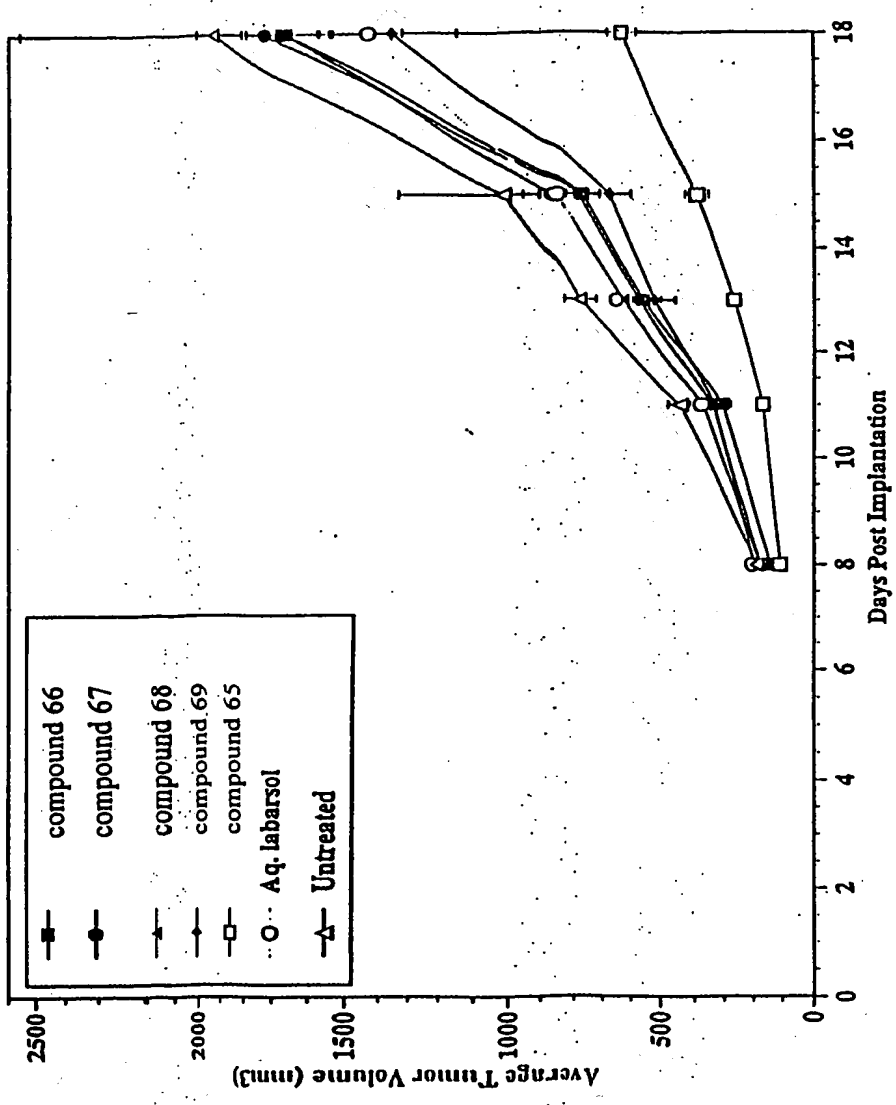


FIGURE 2